PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Abuljadayel et al.
U.S. Serial No.	:	09/568,254
Filing Date	:	May 10, 2000
For	:	A METHOD OF PREPARING AN UNDIFFERENTIATED CELL
Examiner	:	Canella, K.
Art Unit	:	1642

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DECLARATION UNDER 37 C.F.R. §1.132

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Dear Sir:

I, Ilham Saleh Abuljadayel, declare and state that:

1. I am the sole inventor of U.S. application Serial No. 09/568,254 and I am familiar with the application and its prosecution history.

2. A copy of my *curriculum vitae* demonstrating my education, training and experience is appended hereto.

3. I am considered by my peers to be expert in the field to which the application pertains, and am otherwise qualified to speak and render expert opinions as to the present application, invention, and issues of the Final Office Action dated December 3, 2002. Thus,

this Declaration is in response to the Final Office Action.

4. I understand that th Final Office Action of December 3, 2002 rejected all of the claims of the present invention under 35 U.S.C. §101 and §112, alleging that the claimed invention is not supported by a specific, substantial and credible utility. I also understand that the Final Office Action alleges that the application does not provide evidence sufficient to prove that the methods of the invention can be used to induce retrodifferentiation of cells.

5. It is my opinion that these allegations are unfounded. It is also my opinion that the data presented in the instant application, is sufficient to prove that the methods of the present invention can induce retrodifferentiation. Furthermore, in addition to the evidence provided in the present application, I have also performed several other experiments, the results of which confirm by belief that the methods of the present invention can be used to induce retrodifferentiation.

6. Earlier this year I published an article entitled "Induction of stem cell-like plasticity in mononuclear cells derived from unmobilised adults human peripheral blood". A copy of this article, which was published in the peer-reviewed journal Current Medical Research and Opinion, is attached herewith. All of the experiments described in this article were performed by me or under my direct supervision.

The experiments described in this publication involved first obtaining mononuclear cells (MNC) from a human blood sample. These MNCs were obtained by density gradient centrifugation on Histopaque at a specific gravity of 1.077g, a method taught in the present application at page 36, lines 1-4.

As also described in the article, MNCs were subsequently treated with the purified CR3/43 monoclonal antibody (supplied Dako) at a concentration of 3.5μg per ml in order to induce retrodifferentiation. This method is also taught in the present application, on page 19 lines 24-25 and on page 36 lines 18-24.

The data presented in my article demonstrates that, using the methods of the present invention, at least three distinct types of de-differentiated stem cells can be produced. The article demonstrates the generation of:

i) CD34+ haemotopoitic stem cells capable of repopulating non-obese diabetic/severe combined immunodeficient (NOD/SCID) mice;

ii) Neuronal precursor cells that transcribe the primitive stem cell markers OCT-4 and nestin, and which, upon maturation, stain positive for neuronal, glial, or oligodendrocyte-specific markers; and

c) Cardiomyogenic progenitor cells that differentiate into mature cardiomyocytes, and that are capable of synchronous beating, expression of GATA-4, and *in vivo* engraftment.

In this peer reviewed article I conclude that "[t]he induction of stem cell-like plasticity in a heterogeneous population of leukocytes, predominantly comprising mature specialized cells, may have proceeded may a process of retrodifferentiation". To the best of my knowledge, pluripotent stem cells with multi-developmental potential are not present in circulating unmobilised adult human peripheral blood. Therefore, it is my opinion that the data presented in this published article strongly suggests that the methods of the present invention do indeed induce cellular retrodifferentiation.

7. In addition to the above, I have performed additional studies utilizing the methods of my invention, in collaboration with researchers at the George Washington University Medical Center. In these collaborative studies, the NOD/SCID re-populating cells obtained following treatment of MNCs with the CR3/43 monoclonal antibody were characterized. The results of this study will be published in the New Year in the peer-reviewed journal Current Medical Research and Opinion (a pre-print of this article is attached herewith). All of the experiments described in this article were performed either by me or under my direct supervision.

This second study demonstrated that treatment of MNCs with CR3/43, using the methods of the present invention, was sufficient to induce significant human cell engraftment in eighteen out of eighteen NOD/SCID mice, while no such engraftment could be detected in mice infused with untreated MNCs. The article concluded that "the conversion of MNC to SRC in response to treatment with CR3/43 for 3 hr could have far-reaching clinical implications, especially where time and donor-histocompatability are limiting factors". It is my opinion that the untreated MNC preparations described in this article do not contain pluripotent stem cells with multi-developmental potential, and that it is the treatment of the MNCs with the CR3/43 antibody that is responsible for the induction of these cells. It is also my opinion that the induction of pluripotent stem cells in this study occurred by retrodifferentiation.

8. The results of the above studies, taken together with the examples already presented in the instant application, provide strong evidence that the methods of the present

invention do induce retrodifferentiation of cells. Furthermore, the combination of these studies provides compelling evidence that the methods of the present invention have a specific, substantial and credible utility. Therefore, reconsideration and withdrawal of the rejections of the claimed invention under 35 U.S.C. §101 and §112 are respectfully solicited.

9. I further declare that all statements made herein are, to the best of my knowledge, true, and that all statements made on information and belief are believed to be true and further, that these statements have been made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 22-12-2003

Ilham Saleh Abuljadayel